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Is obesity the missing link between COVID-19 severity and air pollution?[☆]



ABSTRACT

Keywords:

Obesity
Air pollution
Covid-19 lethality
Immune system
Main text

In the previous publication “Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?” Conticini et al. hypothesized that the surplus of lethality of the novel SARS-CoV-2 in Northern Italy may be at least in part explained by the evidence of highest pollution reported in this area, as both severe COVID-19 and smog exposure are correlated to an innate immune system hyper-activation with subsequent lung inflammation and injury. Since this hypothesis alone does not fully explain why specific subgroups of patients are at major risk, we hypothesized that obesity may be one of the links between COVID-19 severity and high level of air pollution. First, obesity is a predisposing factor for SARS-CoV-2 infection and worse COVID-19 outcomes, and unequivocal evidence demonstrated that fat mass excess is independently associated with several pulmonary diseases and lung inflammation. Moreover, it has been shown that obesity may intensify the detrimental effects of air pollution on the lungs, and this is not surprising if we consider that these conditions share an excessive activation of the immune system and a lung inflammatory infiltrate. Finally, fat mass excess has also been speculated to be itself a consequence of air pollutants exposure, which has been proved to induce metabolic disruption and weight gain in murine models. In conclusion, although many variables must be taken into account in the analysis of the pandemic, our observations suggest that obesity may act as effect modifier of smog-induced lung-injury, and the concomitant presence of these two factors could better explain the higher virulence, faster spread and greater mortality of SARS-CoV-2 in Northern Italy compared to the rest of the country.

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1. Introduction

In the previous publication “Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?” Conticini et al. investigated the correlation between high lethality of the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the atmospheric pollution in Northern Italy, one of the worst hit areas in Europe by the pandemic (Conticini et al., 2020). In fact, it has been observed that the Northern regions of Lombardy and Emilia Romagna showed death rates of about 12%, unexpectedly higher compared to the rest of the country, where it was around 4.5% (Protezione Civile Italian). In particular, the authors hypothesized that the surplus of lethality in Northern Italy may be at least in part explained by the evidence of highest pollution reported in this area. To note, Fattorini D. & Regoli, F. recently reported data on the distribution of atmospheric pollutants (Nitric Oxide, NO₂; atmospheric particulate matter with a diameter ≤ 2.5 μ m, PM_{2.5}; and atmospheric particulate matter with a diameter ≤ 10.0 μ m, PM₁₀) in Italian regions during the last 4 years, the number of days exceeding regulatory limits, and the years of the last decade (from 2010 to 2019) in which

the limits have been exceeded for at least 35 days. In this regard, they highlighted that Northern Italy has been constantly exposed to air pollution; moreover, air-quality data have been shown to significantly correlate with cases of Coronavirus Disease 19 (COVID-19) in up to 71 Italian provinces providing that chronic exposure to atmospheric contamination may have played a role in facilitating the spread of the virus (Fattorini and Regoli, 2020), and this is not surprising if we consider that atmospheric particulate matter can act as a carrier for many chemical and biological contaminants, including viruses, as they can facilitate their transport and spread (Després et al., 2012). Furthermore, Conticini et al. highlighted that both acute respiratory distress syndrome (ARDS) – one of the worst COVID-19 clinical manifestation, strongly associated with intensive care unit (ICU) and death – and air pollution exposure are correlated to a hyper-activation of the innate immune system, as reflected by the increase of pro-inflammatory cytokines in either serum or lung parenchyma (Conticini et al., 2020). However, this hypothesis alone does not fully explain why particular subgroups of subjects are at major risk of severe manifestation of COVID-19. Therefore, we hypothesized that obesity may represent a further missing link between COVID-19 lethality and air pollution in Northern Italy.

[☆] This paper has been recommended for acceptance by Da Chen.

2. Obesity as predisposing factor for worse COVID-19 outcome

The features most associated with COVID-19 infection and its respiratory complications are male gender, older age, cardiovascular disease, diabetes and higher BMI (Peng et al., 2020; Liu et al., 2020; Coronavirus disease 2019, 2020). Although assessment of obesity is rarely reported in clinical studies, emerging evidence suggest that fat mass excess is associated with either COVID-19 prevalence or severity. In fact, a recent study involving 4103 patients diagnosed with COVID-19 in an academic hospital in the United States proved that a BMI >40 kg/m², suggestive for severe obesity, was one of the strongest predictive factors for hospitalization (OR 6.2) (Petrilli et al., 2020). Moreover, another retrospective study including 103 hospitalized patients with COVID-19, showed that morbid obesity was associated with admission to ICU (Kalligeros et al., 2020), while Simonnet A. et al. reported that weight excess in 124 patients admitted to ICU for SARS-CoV-2 was an independent predictor for the need of invasive mechanical ventilation (Simonnet et al., 2020). Finally, it has been recently proved that abdominal visceral fat is significantly associated with COVID-19 radiological severity and clinical outcomes (Watanabe et al., 2020a). These findings reinforce the hypothesis that obesity represents an independent risk factor for COVID-19 prevalence and severity.

3. Obesity as effect modifier of air pollution-induced lung dysfunction

Several evidence support the hypothesis that a mutual relationship between obesity, air pollution and lung inflammation may exist. First, it is largely known that excessive fat mass is associated with several respiratory pathological conditions, such as asthma, obstructive sleep apnea, obstructive chronic pulmonary disease and ARDS (Mancuso, 1985). The detrimental effects of the increased fat mass on lung could be mediated not only by the anatomical encumbrance of adipose tissue in excess, but also by the low grade systemic inflammation typically associated to obesity (Reilly et al., 2017; Watanabe et al., 2020b); the chronic systemic inflammation on the one hand contributes to the metabolic disruption associated with adipose tissue expansion and on the other hand it can exert detrimental effects on the immune system, making it more susceptible to infections and less responsive to vaccinations, antivirals and antimicrobial drugs (Muscogiuri et al., 2020a). Intriguingly it has recently been observed that adipocytes can accumulate within the lungs of obese subjects, thus generating an abnormal ectopic fat deposition site and exerting a role in enhancing pulmonary inflammatory infiltrate (Elliot et al., 2019), similarly to what happens in the lungs of subjects exposed to air pollutants, as previously highlighted by Conticini et al. (2020). Moreover, if it is largely accepted that air pollution may contribute to the pathogenesis of pulmonary diseases, some studies have also highlighted that the expansion of adipose tissue, namely visceral fat, is strongly associated with air pollution-induced lung dysfunction (Elliot et al., 2019; Conti et al., 2018; Kim et al., 2017; Yang et al., 2019), and this is not surprising considering that both fat excess and air pollution-derived lung injury have been linked to increased local and systemic inflammation (Zhang et al., 2016; Bastard et al., 2000). In this regard, it has been observed in Asian men that obesity may exhibit a synergistic effect on the relationship between prolonged exposure to air pollutants and worse pulmonary function, suggesting that excessive fat, especially the abdominal one, may intensify the adverse effects of air pollutants on lung function (Kim et al., 2017). Another link between air pollution, obesity and COVID-19 severity may be Vitamin D deficiency; obesity is closely associated

with low vitamin D levels, as higher body mass index leads to lower vitamin concentrations (Barrea et al., 2017) and, in light of its largely known and beneficial immunomodulating actions, Vitamin D deficiency may represent an independent risk factor for COVID-19 severity (Muscogiuri et al., 2020b; Grant et al., 2020). Interestingly, air pollution itself predisposes to lower levels of vitamin D, as air pollutants skin deposition prevents local vitamin D synthesis (Kurylowicz, 2011). Taken together these considerations, it appears reasonable to hypothesize that ponderal excess, although not a mediator of air pollution-derived lung injury, may represent an effect modifier of this damage, since obesity can intensify the detrimental effects of air pollutants on the lungs (Corraini et al., 2018).

4. Is obesity a consequence of air pollution?

In addition to representing a contributing factor to the development of smog-induced lung damage, obesity has also been speculated to be itself a consequence of air pollution, although few evidence support this hypothesis. In fact, it is largely accepted that environmental factors, such as the presence of endocrine disrupting compounds (EDCs), play a key role in the pathogenesis of ponderal excess, and specific EDCs, including also inhaled pollutants, are identified as “obesogenic and/or diabetogenic” (Lubrano et al., 2013; Nappi et al., 2016; Darbre, 2015). To interest, a recent metaanalysis found that long-term exposure to ambient air pollution represents a predisposing factor not only for obesity but also for Type 2 Diabetes (Liu et al., 2019). Furthermore, the exposure to Bisphenol A, an organic synthetic compound commonly employed as plasticizer, may exert detrimental effects on glycemic homeostasis (Provisiero et al., 2016). To note, it is largely known that obesity is strongly associated with type 2 diabetes (Al-Goblan et al., 2014), which is itself an independent risk factor for poor prognosis in COVID-19 patients (Peng et al., 2020; Liu et al., 2020; Coronavirus disease 2019, 2020). It has been observed that in Chinese cities, where the smog is alarmingly increasing, the amount of air pollutants and the prevalence of obesity are strongly correlated, especially among older people, suggesting that aged subjects are more sensitive to ambient air pollutants (Yang et al., 2019), which is relevant considering that both advanced age and obesity are major risk factors for COVID-19 severity (Peng et al., 2020; Liu et al., 2020; Coronavirus disease 2019, 2020). Although it is almost impossible to define the causal relationship between obesity and air pollution from epidemiological studies, some evidence deriving from preclinical studies support that air pollutants may represent a direct contributing factor to the pathogenesis of obesity; In fact, air pollutants might act as “obesogens” by altering the methylation of peroxisome proliferator-activated receptor gamma (PPAR γ) or PPAR γ target molecules, known to exert a pivotal role in the regulation of adipogenesis (Janani et al., 2015), or via their binding to the α and β estrogen receptors (ER), actively involved in the regulation of energy metabolism pathways (Chen et al., 2009); furthermore, a recent preclinical study showed that inhaled air pollutants can activate local and systemic inflammatory processes, leading to recruitment of inflammatory cells in adipose tissue with consequent weight gain and metabolic disruption (Zhang et al., 2016); these findings suggest that air pollution may predispose to obesity and its comorbidities in several ways, although prospective population studies are needed to confirm this hypothesis.

5. Obesity, pollution and COVID-19 cases in Italy: an epidemiological analysis

In light of the previous considerations, we would ideally expect a similar trend in obesity prevalence, air quality data and COVID-19

severity in Italy; however, while the incidence of COVID-19 infections, the mortality rate for COVID-19 and mean NO₂, PM_{2.5} and PM₁₀ levels follow a similar trend, as they are higher in the North compared to the South of the country, the prevalence of obesity/overweight seems to behave in the opposite way, being higher in the southern regions compared to the northern ones (Table 1). However, many variables must be taken into account in the interpretation of these data. First, the disparity in obesity prevalence within the country may be explained by the different cultural buffering, socio-economic condition, and the heterogeneous availability of obesity care public services between the northern and southern Italy (Watanabe et al., 2020c); therefore, even if air pollution plays a role in obesity development, this could be limited by the other several factors involved in the pathogenesis of this multifactorial disease. Second, if it is true that the prevalence of ponderal excess is higher in the southern regions, it has also been reported that the population living in the northern ones is older, as expressed by the ageing index, which represent the ratio of elderly persons (aged 65 and over) to the number of young persons (from 0 to 14) (Table 1). Although we do not derive a significant correlation between the ageing index and mortality rate for COVID-19 ($p = .6$), which is influenced itself by several other variables, it is worth recalling that advanced age was previously proved a predictive factor for severe COVID-19 (Peng et al., 2020; Liu et al., 2020; Coronavirus disease 2019, 2020). Furthermore, Italian regions adopted different health policies in the management of the pandemic, and this has certainly influenced the spread of Sars-Cov2 infection; for example, in Veneto, despite the higher NO₂, PM_{2.5} and PM₁₀ levels in the weeks preceeding SARS-Cov2

outbreak and the greater prevalence of overweight/obesity, there were lower cumulative incidence of Covid-19 cases and mortality compared to Lombardia. However, although the two regions adopted similar approaches in terms of social distancing and retail closures, Veneto proceeded towards a more proactive strategy for the containment of the virus, with a policy based on extensive testing of both symptomatic and asymptomatic cases, whereas Lombardy opted instead for a more conservative approach to testing, with a stronger focus only on symptomatic cases (Romagnani et al., 2020). It is likely that the different regional policies may have overestimated the mortality data reported in Lombardy compared to Veneto, making data related to virus lethality uncertain and difficult to interpret. Furthermore, it has been reported that in Lombardia, where during the pandemic outbreak hospitals were overcrowded and contaminated, and medications, mechanical ventilators, oxygen, and personal protective equipment were not available, home care and mobile clinics have been encouraged (Nacoti et al., 2020); on the other hand, it is reasonable to hypothesize that in Veneto, where the pandemic did not reach the same frightening proportions, a more patient-centered care strategy has been adopted. The different health-care strategies adopted by the two neighboring regions could explain the milder impact of the pandemic and the lower virus lethality in Veneto in comparison to Lombardia, despite the higher air pollution levels and overweight/obesity prevalence (Table 1). Intriguingly, when we analyzed specific sub-regions of Lombardia, in which comparable health policy strategies were adopted, we noted that in Bergamo, by far the most affected by the pandemic, PM_{2.5} and PM₁₀ levels registered between February 10 and March 10 were 35.4 $\mu\text{g}/\text{m}^3$

Table 1
Covid-19 cumulative incidence per 100,000 inhab., NO₂, Mortality rate for COVID-19 standardized per 100,000 inhab., PM_{2.5}, PM_{10.0} mean levels registered from the 10th of February to the March 10, 2020, Overweight/Obesity prevalence and Ageing Index in Italian Regions.

| Regions | COVID-19 Cumulative Incidence per 100,000 inhab. ^a | Mortality rate for COVID-19 standardized per 100,000 inhab. ^b | NO ₂ ($\mu\text{g}/\text{m}^3$) ^c | PM _{2.5} ($\mu\text{g}/\text{m}^3$) ^c | PM _{10.0} ($\mu\text{g}/\text{m}^3$) ^c | Overweight and/or Obesity Prevalence (%) ^d | Ageing Index ^e |
|-----------------------|---|--|---|---|--|---|---------------------------|
| Piemonte | 722.15 | 39.8 | 30.88 | / | / | 37.5 | 210.3 |
| Emilia-Romagna | 629.76 | 64.1 | 31.91 | / | 41.29 | 42.4 | 185.6 |
| Veneto | 301.8 | 26.4 | 33.52 | 42.88 | 71.74 | 40.6 | 177.6 |
| Toscana | 267.59 | 17.4 | 29 | 15.63 | 26.76 | 36.4 | 209.1 |
| Liguria | 635.42 | 51.3 | / | / | / | 34.3 | 260.4 |
| Lazio | 136.04 | 8.2 | 33.57 | 15.28 | 32.41 | 40.3 | 167.3 |
| Marche | 442.35 | 42.4 | 23.68 | 26.53 | 48.53 | 42.3 | 201.8 |
| Campania | 79.7 | 6.4 | 22.9 | 23.01 | 37.02 | 50.9 | 134.7 |
| Puglia | 112.09 | 9.3 | 11.4 | 15.73 | 25.65 | 45.8 | 175 |
| Trentino | 1007.77 | 57.2 | 48.18 | 20.35 | 32.15 | 34 | 142.4 |
| Sicilia | 61.54 | 4.2 | 25.28 | / | / | 46.6 | 158.6 |
| Friuli-Venezia Giulia | 273.61 | 17.9 | 15.46 | / | 44.9 | 41 | 223.2 |
| Abruzzo | 250.23 | 19.4 | 34.7 | 22.05 | 33.25 | 44.6 | 197.6 |
| Alto Adige | 489.29 | 57.2 | 41.54 | / | / | 34.7 | 127.2 |
| Umbria | 162.81 | 5.4 | 25.46 | 20.67 | 26.04 | 43 | 209.6 |
| Sardegna | 82.7 | 6.5 | 19.28 | / | / | 38.8 | 221.2 |
| Calabria | 59.11 | 4.3 | 17.31 | 10.94 | 21.67 | 48.4 | 168.3 |
| Valle d'Aosta | 953.32 | 94.1 | / | / | / | 37.8 | 187.2 |
| Molise | 143.64 | 4.4 | 15.03 | / | / | 48.4 | 224.8 |
| Basilicata | 65.02 | 2.6 | / | / | 17.1 | 51.3 | 200.3 |

Abbreviation: COVID-19, Corona Virus Disease 2019; inhab., 206 inhabitants; NO₂, nitric oxide; PM_{2.5}, atmospheric particulate matter with a diameter ≤ 2.5 μm ; PM_{10.0}, 207 atmospheric particulate matter with a diameter ≤ 10.0 μm .

^a **COVID-19 Cumulative Incidence per 100,000 inhab.:** number of new cases per 100,000 inhab. From March 3 to June 19, 2020 (Ministero della Salute (www.salute.gov.it), updated to June 19, 2020)

^b **Mortality rate for COVID-19 standardized per 100,000 inhab.:** adjustment of the mortality rate that allows to compare populations having different age distributions; the standardization method by age consists of summarizing the mortality rates calculated for each specific age group on a standard population (in this case the Italian population at Census, 2011) (Report on impact of the 197 Covid-19 epidemic on the total mortality, Istat, June 4, 2020)

^c European Environment Agency (<https://www.eea.europa.eu/themes/air/air-quality-and-covid19/monitoring-covid-19-impacts-on>) updated to June 29, 2020.

^d Studio Passi (2015–2018)

^e **Ageing Index:** the ratio of elderly persons (aged 65 and over) to the number of young persons (from 0 to 14) (Istat, Indicatori Demografici 2020)

and 43.8 $\mu\text{g}/\text{m}^3$, higher than the mean regional ones, and overweight/obesity prevalence was 36.2% (Press release 61/2019 8/1, 2019), which is still higher than the one reported in Lombardia (Table 1). These data suggest that other variables in association to obesity and pollution should be taken into consideration in the analysis of the pandemic trend, but they do not exclude that the two factors may act synergistically to facilitate the spread and severity of COVID-19.

6. Conclusion

The high degree of smog has been proposed as an explanation for the increased COVID-19 severity in Northern Italy, strengthened by the observation that ARDS and smog-induced lung damage share similar pathogenetic mechanisms involving a hyperactivation of the innate immune system. However, this hypothesis alone does not fully explain why particular subgroups of subjects, such as elderly and obese patients, are at major risk of severe manifestation of COVID-19. In the current correspondence, we suggested that obesity may be one of the missing piece to complete this puzzle. In fact, in addition to representing a predisposing factor for COVID-19 infection and worse clinical outcomes, fat mass excess has also been associated to increased pulmonary and systemic inflammation, similarly to what happens in the lungs of subjects exposed to air pollutants and of patients diagnosed with COVID-19. In particular, obesity may be considered as an effect modifier of smog-derived lung injury, since its presence intensifies the detrimental effects of air pollutants on the lungs and it predisposes to Sars-Cov-2 infection and severity. Although several variables, such as age and health care policies, must be taken into account in the analysis of the pandemic trend, our observations suggest that ponderal excess and air pollution may act synergistically to contribute to severe COVID-19, and that the concomitant presence of obesity together and air pollution could better explain the higher virulence, faster spread and greater mortality of SARS-CoV-2 in Northern Italy compared to the rest of the country.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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